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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,524	01/04/99	SONE T	SPO-103

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EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	16

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/142,524	Sone et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on May 19, 2000 and 4/17/00

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1 and 3-30 is/are pending in the applicat

Of the above, claim(s) 8, 9, 14-16, and 27-30 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 3-7, 10-13, and 17-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendments, filed 5/19/00 and 4/17/00 (Papers No. 15 and 13, respectively), are acknowledged and have been entered.

2. Upon consideration of the citing of prior art that reads upon "contains an amino acid sequence described in" SEQ ID NO: 1, 2 or 3, claims 11, 12, 23 and 24 are hereby rejoined to the elected Group.

Accordingly, claims 8, 9, 14-16 and 27-29 (non-elected species) and claim 30 (a non-elected invention) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 3-7, 10-13 and 17-26 are presently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

a. the oath contains a claim under both domestic and foreign priority for PCT/JP97/00740.

b. The filing date of the instant application is 1/4/99, whereas the filing date listed in the oath is 9/9/98.

The following are new grounds of rejection necessitated by the amendment filed 4/17/00.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-7, 10-13 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant specification and claims as originally filed do not support the following limitations:

a. In claim 1, at line 4, "via a peptide bond". The specification on page 8 at lines 2-16 discloses that "The "multi-epitope peptide" used herein means a peptide molecule prepared by linearly joining peptides containing T cell epitopes derived from different allergen molecules (sometimes referred to as an antigenic peptide or merely as a peptide)". The specification then goes on to disclose, "In this peptide, a region that is cleaved in vivo is preferably inserted between the T cell epitope-containing peptides to minimize the occurrence of epitope sites that are newly recognized." Although the instant specification discloses linearly joining peptides, it does not disclose doing so "via a peptide bond."

b. In claim 1, at lines 11-12, "said multi-epitope peptide reacts dose-dependently with peripheral blood lymphocytes from the patient sensitive to the allergens."

c. In claim 1, at lines 15-17, "each of said T cell epitope peptides is restricted by at least two molecules of HLA class II molecules of the patient sensitive to the allergens, selected from the group consisting of DP, DQ, and DR antigens." The instant specification discloses on page 7 at lines 6-14 selecting T cell epitope peptides that are from different HLA haplotypes that appear in the population of patients (including different races). "T cell epitope peptides were selected noting that those binding to HLA whose haplotype frequently appears in the population and those presented on different HLA class II molecules, not the same HLA class II molecule, should be selected. The thus-selected multi-epitope peptides were clarified to be effective for a wider range of patients." The specification on the paragraph bridging pages 43 and 44, discloses that "It [the multi-epitope peptide] contains the peptide presented on the HLA class II molecule encoded by the gene that frequently appears in the population of patients with allergy...It further contains several peptides presented on the HLA class II molecules in different loci (DR, DQ, DP)." The instant specification discloses on pages 10 and 11 choice of peptide epitopes based upon the frequency of class II HLA alleles in certain races. Instant claim 7 recites a peptide-based immunotherapeutic agent wherein said peptide contains an epitope restricted by at least one HLA class II molecule recited in said claim. However, the specification and claims as filed do not support the limitation that each T cell epitope peptide is restricted by at least two class II HLA molecules of the patient sensitive to the allergens.

d. In claims 10 and 18, at lines 1-2, "wherein the allergen-specific IgE antibodies do not cross-react with the different allergen molecules."

e. In claims 13 and 26, at lines 1-3, "wherein each of said T cell epitope peptides consists of minimum core sequences with retaining effective T cell reactivity."

Applicant has not pointed to support in the specification and claims as filed for the amendments

to the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 13 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 13 and 26 are indefinite in the recitation of "wherein each of said T cell epitope peptides consists of minimum core sequences with retaining effective T cell reactivity" because it is not clear what is meant.

9. Claim 1 is indefinite in the recitation of "each of said T cell epitope peptides is restricted by at least two molecules of HLA class II molecules of the patient sensitive to the allergens, selected from the group consisting of DP, DQ and DR antigens" because it is not clear what is meant. Does patient sensitive to the allergens mean an individual patient, or a group of patients, as in a population of the same or different race?

10. Claims 6 is indefinite in the recitation of "contains an amino acid sequence described in any of SEQ ID NO: " because it is not clear what is meant.

11. Claims 11, 12, 23 and 24 are indefinite in the recitation of "wherein said peptide contains an amino acid sequence described in SEQ ID NO: " because it is not clear what is meant.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3-7, 10-13 and 17-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al (Molecular Immunology, Vol. 31 (13) pp 955-966, 1994, entire document) in view of WO 94/01560 (20 January 1994, pages 1-106) and further in view of Hashiguchi et al (Peptide Chemistry, Volume 33, 1996, pages 409-412) or Komiyama et al (Biochemical and Biophysical Research Communications, Volume 201, 1994, pages 1021-1028) or WO 94/11512, and Wallner et al (Allergy, Volume 49, 1994, pages 302-308).

Rogers et al teach a peptide-based immmunotherapeutic agent comprising a linear multi-epitope linear polypeptide with different T cell epitope regions joined to each other, wherein said polypeptide does not substantially react with allergic human IgE, wherein said different T cell epitope regions are derived from two or more different allergen molecules and wherein said polypeptide reacts with peripheral lymphocytes from at least not less than 70% of said population patients sensitive to said allergen(s) (especially Abstract; page 956; Table 2; page 961, column 1, second full paragraph; page 963, column 1, lines 6-9; page 964, column 1, first two full paragraphs; page 964, column 2, lines 24-29 and lines 60-71; page 965, lines 1-2). Rogers et al teach that their approach to a peptide-based immunotherapeutic agent can be generally applicable to the combination of multiple T cell epitope-containing sequences from one or more antigens into a single polypeptide chain, that a single antigen can have multiple T cell epitopes recognized in the atopic human population, and that the polypeptide can also be constructed using T cell epitopes from unrelated antigens or allergens from diverse sources page 964, lines 60-71 and continuing onto page 965, lines 1-2). Rogers et al inherently teach said immunotherapeutic agent wherein each of the T cell epitope regions shows a positivity index of not less than approximately 100 when measured in a population of patients sensitive to allergen(s) (especially Figure 5 and page 961, column 2, lines 5-17), see below. Rogers et al teach that making said T-cell epitope-containing peptides which have significantly reduced reactivity with allergic human IgE is a novel and useful therapeutic approach for desensitization to important allergens.

Rogers et al do not teach said immunotherapeutic agent supra wherein the T cell epitope regions are comprise different allergen molecules that are cedar pollen allergens Cry j 1 and Cry j 2. Rogers et al do not teach said immunotherapeutic agent wherein a site that is processed in the antigen-presenting cells is inserted between each of the T cell epitope regions, and wherein said site is an arginine dimer (R-R) or a lysine dimer (K-K). Rogers et al do not teach said agent wherein said peptide contains an epitope restricted by at least one HLA-Class II molecule selected from those recited in instant claim 7.

The WO 94/01560 document teaches linear polypeptides comprising at least two different T cell epitope regions from Cry j 1 joined to each other which do not substantially react with allergic human IgE (especially Abstract, page 4, lines 17-24, page 13, lines 12-20). The WO 94/01560 document teaches said polypeptides have epitope regions with positivity indices of at least about 100 (especially page 28, lines 19-32) and teaches that positivity index for a peptide

is determined by multiplying the mean T cell stimulation index by the percent of individuals in a population sensitive to allergen (preferably at least 15 individuals), who have a T cell stimulation index to such peptide of at least 2.0. The WO 94/01560 document teaches that stimulation index for T cells to peptides can be calculated as the maximum CPM in response to a peptide divided by the control CPM (especially page 28, lines 2-5). WO 94/01560 teaches that peptides are selected based upon various factors including the frequency of the T cell response to the peptide in a population of individuals sensitive to the allergens and the strength of the T cell response to the peptide. It also teaches pharmaceutical compositions containing these polypeptides which comprise a sufficient percentage of the T cell epitopes such that at least about 60% of the T cell reactivity of the allergens are included in the composition. WO 94/01560 teaches that charged amino acid pairs such as KK or RR can be introduced between T cell epitope regions and that the resulting peptide is rendered sensitive to capthepsin and/or other trypsin-like enzymes which are involved in processing of T cell epitopes in vivo (especially page 24, lines 5-13). WO 94/01560 teaches peptides comprising at least two regions, each region comprising at least two T cell epitopes of a Japanese cedar pollen protein allergen or comprising epitopes from peptides which are immunologically related (especially page 26, lines 25-31). The WO 94/01560 document also teaches a method for determining which peptides from cry j 1 or another allergen have T cell epitope regions (especially page 27, lines 19-32 and continuing onto page 28, lines 1-5). WO 94/01560 teaches a peptide CJI-22 (211-230) which has the sequence KSMKVTVAFNQFGPNCGQRM (especially figure 13). Said peptide contains an amino acid sequence described in SEQ ID NO: 1, 2 and 3 (underlined).

Hashiguchi et al teach T cell epitopes of Cry j 2.

WO 94/11512 teaches purified Cry j 2 protein, and T cell epitopes thereof, a method of producing the protein and epitopes and a method of identifying T cell epitopes, and the usefulness in treatment, diagnosing and preventing Japanese cedar pollinosis (especially Abstract, page 14, lines 35-36 and continuing onto page 15, lines 1-6 and lines 17-37 and page 16, lines 1-36).

Komiyama et al teach the deduced amino acid sequence of Cry j 2, the second major allergen of Japanese Cedar Pollen, Cry j 1 being the first (especially Abstract and page 1021 and first paragraph of page 1022). Komiyama et al teach that amino acid sequence information for Cry j 2 is useful for the determination of T cell epitopes from that allergen (especially page 1027, lines 3-8). Komiyama et al teach that patients suffering from pollinosis have IgE antibodies specific for Cry j 1 and Cry j 2 (especially page 1022, lines 7-8) and the usefulness of recombinant Cry j 2 protein for immunotherapy (especially page 1027, lines 8-10).

Wallner et al teach that the diversity of the human population with respect to its HLA haplotype has to be taken into account in defining clinical peptide candidates. Wallner et al

teach that permissive interaction between peptides and several HLA alleles probably accounts for the observation that peptides containing the major T-cell epitope of an allergen cause T-cell responses in 80-90% of the allergic population and that clinical peptide candidates therefore have to be designed to cover the diverse HLA haplotype of the allergic patient population.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a multi-epitope immunotherapeutic agent such as the one taught by Rogers et al with the regions joined to each other via peptide bond using the cryj1 peptides of WO 94/01560 and cry j2 peptides deduced from the teachings of Hashiguchi et al and Komiyama et al, respectively, given the teaching of Rogers et al that a multi-epitope peptide can be constructed using T cell epitopes from allergens from diverse sources. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make T-cell epitope-containing peptides which have significantly reduced reactivity with allergic human IgE for use in desensitization to important allergens, such as treatment of pollenosis caused by Japanese Cedar Pollen, as taught by Rogers et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed a multi-epitope peptide using lysine or arginine dimers that can be introduced between T cell epitope regions to serve as a site that is processed in antigen-presenting cells given the teaching of WO 94/01560. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to enhance processing of the epitopes for presentation by HLA as taught by WO 94/01560.

During examination, claims are given their broadest reasonable interpretation. Instant claims 1, 3-7, 10-13 and 17-26 are included in this rejection because it would have been obvious to one of ordinary skill at the time the invention was made: to have made an immunotherapeutic agent comprising an amount effective to prevent or treat allergic symptoms of allergic patients; T cell epitopes are by definition reactive with T cell clones; to have made an immunotherapeutic agent that reacts dose-dependently; in a population of allergic patients, selected said T cell epitopes that interact with more than one HLA haplotype selected from DP, DQ and DR, particularly given the teaching of Wallner et al supra; to have determined the minimal epitope, i.e., minimum core sequences, for T cell epitopes restricted by particular HLA haplotypes; to have selected epitopes that provide the greatest possible protection, i.e., do not cross-react with IgE antibodies to the other epitopes. Claims 6, 11, 12, 22, 23 and 24 are included because WO 94/01560 teaches a peptide CJI-22 (211-230) which has the sequence KSMKVTVAFNQFGPNCGQRM. Said peptide contains an amino acid sequence described in SEQ ID NO: 1, 2 and 3.

Applicant's arguments filed 4/17/99 have been fully considered but they are not persuasive.

Regarding Applicant's arguments on Rogers et al on pages 8 and 9 of said amendment, i.e., that Rogers et al fail to teach polypeptides which do not substantially react with IgE antibodies found in the sera of allergic patients based upon Figure 3, in which two out of six multi-epitope peptides react qualitatively in Western Blot with "allergic sera" containing IgE antibodies, whereas all six peptides of the instant invention (pages 31 and 32 of the instant specification at Example 7 and Figure 8) "failed to substantially react with immune sera of tested individuals." Rogers et al only used the sera of only *one* patient in the Western Blot of Figure 3 on page 961, whereas the claimed invention used 29 patients sera in ELISA assay and on page 31 of the specification, see lines 18 to bottom of page. Fluorescent intensity is cited as 3-5 for all 29 patients with all six of the multi-epitope peptides as evidence for "failing to substantially react", but the control, i.e., native Cry j1, in five subjects was 9, and in four subjects it was 10, in 14 subjects it was 100. Since no standard deviation values are given, the statistical significance of the claimed invention with regard to "fail to substantially react" with IgE from allergic individuals can not be assessed. Furthermore, it is unlikely that a fluorescence intensity of 9 is statistically different from one of 3-5.

With regard to Applicant's argument on page 8 of amendment filed 4/17/00, only a reasonable expectation of success by one of ordinary skill in the art is required. Rogers et al teaches on page 965, "Conceivably, recombined T cell epitope-containing polypeptides can also be constructed using T cell epitope sequences derived from unrelated Ag or even allergens from diverse sources."

In addition, with regard to Applicant's comments on page 12 regarding motivation to choose epitopes from cry j1 and cry j2 from among all the pollen allergens, as discussed supra, Komiyama teach that cry j2 is the second major allergen of Japanese Cedar Pollen, cry j1 being the first. Komiyama et al further teach that patients suffering from pollenosis due to Japanese Cedar Pollen have IgE antibodies specific for cry j1 and cry j2. It would have been obvious to the skilled artisan at the time the invention was made to have combined epitopes from these two major allergens of Japanese Cedar Pollen in order to more effectively treat or diagnose pollenosis due to Japanese Cedar Pollen.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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